U.S. Department
of Transportation
**Research and
Special Programs
Administration**

400 Seventh St., S.W.
Washington, D.C. 20590

NOV 3 2004

Mr. Jeff Griebel, BS, RRT
Medical Affairs Department
INO Therapeutics, LLC
6 State Road 173
Clinton, NJ 08809

Ref. No.: 04-0162

Dear Mr. Griebel:

This responds to your letter regarding the use of nitric oxide on air medical transports in accordance with the Hazardous Materials Regulations (HMR; 49 CFR Parts 171-180). You enclosed a Material Safety Data Sheet, specifications for the delivery device (cylinder), and several documents containing additional technical information. You provided information, as follows:

> INO Therapeutics markets the drug INOmax®, nitric oxide for inhalation, which is used to treat severely ill newborn infants with lung disease. The drug INOmax® is an FDA approved medication for inhalation in infants. When a patient is transferred from one hospital to another, any attempt to withdraw this drug, even for a short duration, may lead to a sudden worsening of the patient's condition or even death. Because "Nitric oxide, compressed" is listed in the HMR as a Division 2.3 material (poisonous gas) and is poisonous by inhalation, it is forbidden aboard passenger-carrying and cargo-only aircraft.
>
> The drug INOmax® consists of a very low concentration of nitric oxide, 0.08% (800 ppm), and 99.92% nitrogen (non-flammable gas). The 800 ppm concentration of nitric oxide is below the criteria for hazard zones A, B, C, or D for Division 2.3 gases. At a concentration of 0.08% of nitric oxide and 99.92% nitrogen, your company's opinion is that the pharmaceutical grade of the drug meets the definition of a Division 2.2 (non-flammable gas) material.
>
> Nitric oxide is delivered to patients using a special delivery device that has been tested to military standards to be flight compatible, and meets the exceptions for transportation of incubators as specified in § 175.10 of the HMR. The delivery device is a cylinder ("D Size Cylinder") having a diameter of 4.5", total height of 20.5", weight of 8 pounds empty and 9 pounds full, pressure is 2000 psi (maximum), gas capacity is 370 liters of usable gas filled @ 2000 psi, and water capacity is 2.818 liters. The "D size cylinders" do not have valve protection caps, valve protection headbands or headrings, and must be securely packed in strong packaging to adequately protect the valves arid fittings.

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173.115

Specifically, you asked for our opinion on the correct classification of the drug INOmax® at a concentration of 0.08% of nitric oxide and 99.92% nitrogen.

It is the opinion of this Office that a compressed gas mixture containing 0.08% nitric oxide and 99.92% nitrogen meets the definition in § 173.115 of the HMR for a Division 2.2 (non-flammable, nonpoisonous, compressed gas) material. Nitric oxide is also listed in the Hazardous Materials Table, Appendix A, Table I, as a hazardous substance if shipped in a reportable quantity (RQ) of 10 pounds or more per package (see § 171.8). A material described as "Compressed gas, n.o.s., 2.2, UN1956" is regulated for purposes of transportation in commerce when carried aboard commercial aircraft.

As provided in § 175.10(a)(14), a transport incubator unit that is necessary to protect life is not regulated under the HMR when transported by aircraft when the following conditions are met: (1) the compressed gas used to operate the unit is in an authorized DOT specification cylinder and is marked, labeled, filled and maintained as prescribed by the HMR; (2) each battery used in its operation is of the non-spillable type; (3) the unit is constructed so that valves, fittings, and gauges are protected from damage; (4) the pilot-in-command is advised that the unit is onboard and when it is intended for use; (5) the unit is accompanied by a person qualified to operate it; (6) the unit is secured in the aircraft in a manner so as not to restrict access to or use of any required emergency or regular exit or of the aisle in the passenger compartment; and (7) smoking within 3 m (10 feet) of the unit is prohibited.

An incubator unit as described above using a Division 2.2 (non-flammable gas) compressed gas mixture is not subject to the HMR and not regulated for air transport when the above conditions are met. If your company's device containing the drug INOmax® meets all of the conditions under the exception in § 175.10(a)(14), it may be transported on both passenger and cargo-only aircraft.

I hope this information is helpful. If we can be of further assistance, please contact us.

Sincerely,

John A. Gale
Chief, Standards Development
Office of Hazardous Materials Standards

INO Therapeutics, LLC
6 State Road 173
Clinton, NJ 08809
908-238-6600

Engram
§173.306
§173.115
Limited quantities of
Compressed Gases
04-0162

John Gale
US Department of Transportation
Office of Hazardous Materials Standards
407th Street SW
Washington, DC 20590

Mr Gale,

This letter is a follow up to our phone conversation regarding the use of nitric oxide on air medical transports. As I mentioned, INO Therapeutics, LLC markets the drug INOmax®, nitric oxide for inhalation, which is used to treat severely sick newborn infants with lung disease. When a patient is transferred from one hospital to another, any attempt to withdraw this drug, even for a short duration, may lead to a sudden worsening of the patient's condition or even death. It is important that emergency medical transport teams are allowed to carry and use this drug while in flight.

There are over 100 emergency medical transport teams that now provide nitric oxide as a treatment. The problem we often encounter is interpretation of the hazardous materials standards by some pilots and Federal Aviation Administration inspectors. Because nitric oxide is listed in the DOT manual as a division 2.3 gas (poisonous by inhalation), it cannot be carried on an aircraft. The pharmaceutical grade of nitric oxide we supply to treat patients is packaged in a very low concentration, 0.08% (800 ppm) in a balance of nitrogen gas. The 800 ppm concentration of nitric oxide is well below hazard zones A, B, C, and D used for division 2.3 gases. At this concentration, nitric oxide is actually a division 2.2, UN 1956 (non-flammable, non poisonous) gas and should be reasonably safe to carry on an aircraft, especially since it is an FDA approved medication for inhalation in infants. I will enclose a summary of the cylinder characteristics and our MSDS with this letter for further reference. We feel that it is important to provide accurate information to pilots and FAA inspectors and we are requesting an interpretation on the hazardous materials standards for this concentration of nitric oxide.

Nitric oxide is delivered to patients using a special delivery device that has been tested to military standards to be flight compatible. It also meets the requirements of transport incubators as specified in CFR 49, section 175 of the DOT hazardous materials standards. Can you let us know if there is a need for an interpretation on the delivery device itself, or is that an issue we should discuss with the FAA?

We would appreciate an interpretation on the hazardous materials standards for pharmaceutical grade nitric oxide in the form of a letter. We would like to supply a copy of this letter with the training materials that we give to hospitals when they begin transporting patients using inhaled nitric oxide.

Thank you for offering to put me in touch with the appropriate FAA officials in order to obtain their opinion on this subject as well. Please let me know how to proceed

with this step when appropriate. I am also available to meet with anyone you feel will contribute to this process. Again, thank you for your kind assistance.

Best regards,

Jeff Griebel

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Medical Affairs Department
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Pager 800-718-7263

Mailing Address:
Jeff Griebel
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Enclosed:
Cylinder description
Materials Safety Data Sheet (MSDS)
INOmax® (nitric oxide for inhalation) package insert
Publication: Use of Inhaled Nitric Oxide During
Interhospital Transport of
Newborns With Hypoxemic
Respiratory Failure
Delivery device description

Cc Barry Price
Robert McConnell